PAPERS AND SHORT REPORTS

Mass vaccination programme aimed at eradicating measles, mumps, and rubella in Sweden: first experience

BRITH CHRISTENSON, MARGARETA BÖTTIGER, LEO HELLER

Abstract

General vaccination with a combined measles, mumps, and rubella vaccine was introduced in Sweden in 1982. The immunisation schedule comprises two vaccine injections, given at 18 months and 12 years of age, respectively. A controlled field study was carried out in 150 children aged 18 months using two different batches of the vaccine. Seroconversion was seen in 96% against measles, 93% against mumps, and 99% against rubella —the same rates with both vaccine lots. Nevertheless, a difference was noted between the two batches with respect to postvaccination reactions. Fever and rash were recorded mainly five to 12 days after vaccination. Moderate fever (38·5-39·4°C) was observed in 22 children, high fever (≥39·5°C) in 33, and rash in 35. Preliminary results obtained by follow up of routinely vaccinated schoolchildren aged 12 indicated considerably lower rates of fever and rash during the postvaccination period, occurring in 3-10% of cases only.

These findings show that complete eradication of measles, mumps, and rubella in Sweden is entirely practicable by the mass vaccination programme and that side effects of vaccination are likely to be few and mild.

Introduction

In 1982 a new strategy for immunisation against measles, mumps, and rubella was introduced in Sweden, which was expected to give more complete protection at all ages within relatively few years.[1] The vaccination schedule includes two injections of the combined vaccine, given at 18 months and 12 years of age. Vaccinating at 18 months only was abandoned because of the risk of increasing numbers of people remaining unprotected among those left unvaccinated or who had failed to seroconvert after the first injection.[2] It was also feared that as younger, already vaccinated and predominantly immune age groups stopped being the usual source of infection older, unvaccinated children and adolescents would no longer be exposed to the natural wild infections.

The ultimate aim of the new strategy is rapid elimination of all three diseases. To assess the rate of seroconversion and the occurrence of clinical reactions after injection of the commercially available combined vaccine we carried out a controlled trial in 150 children aged 18 months. Clinical reactions after vaccination of schoolchildren were assessed over a longer period but less rigorously.

Material and methods

Vaccine—The combined vaccine contained the Moratan (measles), Jeryl Lynn (mumps), and RA 27/3 (rubella) live attenuated virus strains.[3] Half of the children received a batch of the vaccine provided by Merck, Sharp, and Dohme Research Laboratories, USA (lot 3259 D; vaccine A), and the other half a commercial lot of the same vaccine marketed in Europe (lot 6225; vaccine B). The incidences of fever and rash caused by the vaccines were subsequently compared with similar data obtained after the start in 1982 of the general vaccination campaign in 18 month old children with two further lots of the same vaccine (lot 002-1 (vaccine C) and lot 003-1 (vaccine D)).

Plan of study—Four well baby clinics in central Sweden participated in the trial. The two vaccine lots (A and B) were given at random to 150 children; 77 received vaccine A and 73 vaccine B. Owing to ethical regulations in Sweden, no unvaccinated control group could be included. All parents completed a written consent form for vaccination and blood sampling. A first blood sample (0·4 ml) was drawn from a finger immediately before vaccination and a second sample drawn two months later. Parents were provided with a questionnaire on which to keep a daily record of their child's health and possible ailments during the month after vaccination. Leading questions were not used. The parents measured the child's temperature only if he appeared feverish. The trial was approved by the ethical board of the Karolinska Institute, Stockholm.

Serological testing—Measles antibodies were measured by a con-

Department of Epidemiology and Vaccine Department, National Bacteriological Laboratory, S 105 21 Stockholm, Sweden

BRITH CHRISTENSON, MD, acting assistant professor, department of epidemiology

MARGARETA BÖTTIGER, MD, professor, director, department of epidemiology

LEO HELLER, MD, assistant professor, vaccine department

Correspondence to: Dr Brith Christenson.

ventional haemagglutination inhibition test performed on microplates.[4] The lowest initial dilution tested was 1/10. Antibodies against mumps were evaluated both by the serum neutralisation test on microplates (initial serum dilution 1/2)[5] and by the haemolysis in gel technique. Antibodies against rubella were assayed by the haemolysis in gel method.[6] Zone diameters of 6 mm or more were taken as positive.

Statistical analysis was by Student's *t* test.

Results

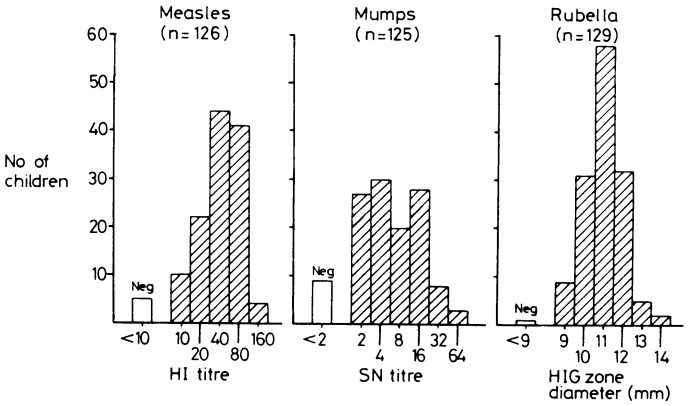
CLINICAL FINDINGS

Questionnaires on clinical reactions during the four weeks after vaccination were returned for all 150 children immunised with the two batches of vaccine (table I). Fever and rash occurred mainly five to 12 days after vaccination. Moderate fever (38·5-39·4°C) was observed in 22 children and fevers of 39·5°C and over in 33. No complaints were noted after day 19.

A discrete, morbilliform rash was reported in 35 children. Fever of 39·5°C and over was accompanied by febrile convulsions in two cases. Other symptoms, including swelling of cervical lymph nodes or parotid gland, conjunctivitis, and cough, were reported in a few children. Vaccine B produced significantly more complaints than vaccine A ($p < 0.001$) (table I).

Table II compares the incidences of fever and rash caused by vaccines A and B with similar data obtained after beginning the general vaccination campaign with the two further batches of vaccine (C and D).

Mumps—Only one of the 141 sera tested by haemolysis in gel and five of 130 tested by serum neutralisation showed positive activity against mumps before vaccination. Of the remainder, 129 (92%) and 116 (93%) respectively showed seroconversion by the two tests after vaccination. The figure shows the distribution of postvaccination serum neutralisation titres. The comparability of the two techniques



Frequency distribution of postvaccination antibody state against measles (haemagglutination inhibition (HI) titres), mumps (serum neutralisation (SN) titres), and rubella (haemolysis in gel (HIG) zone diameters) in 18 month old children as assessed two months after immunisation. (Children were predominantly seronegative before vaccination.)

TABLE I—*Signs and symptoms in 150 young children immunised with two alternative lots of combined vaccine during first four weeks after vaccination. Result expressed as numbers of children*

	Vaccine A (lot 3259 D)				Vaccine B (lot 6225)				Both vaccines (pooled groups)				Grand total (No (%))
No of questionnaires	77				73				150				
No (%) of children reporting one or more complaints	26 (34)*				46 (63)*				72 (48)				
	No of days after immunisation†			Total	No of days after immunisation†			Total	No of days after immunisation				
	0–4	5–12	13–28		0–4	5–12	13–28		0–4	5–12	13–28		
Fever 38·0–38·4°C	1	3		4		3		3	1	6			7 (5)
Fever 38·5–39·4°C	1	8	1	10	2	8	2	12	3	16	3		22 (15)
Fever ≥39·5°C	1	9		10‡	2	21		23‡	3	30			33 (22)
Rash	1	11		12§	2	19	2	23§	3	30	2		35 (23)
Febrile convulsions		1		1		1		1		2			2 (1)
Cervical lymphadenitis or parotitis		2		2		2		2		4			4 (3)
Ocular complaints	1	3		4		3		3	1	6			7 (5)
Cough		2		2		3		3		5			5 (3)

*Difference between vaccine lots significant at $p < 0.001$ level.
‡Difference between vaccine lots significant at $p < 0.01$ level.
†Date of onset or day when highest body temperature was recorded.
§Difference between vaccine lots significant at $p < 0.05$ level.

TABLE II—*Frequency of feverish reactions and rash after vaccination of 18 month old children in Sweden with four different lots of combined vaccine. Results expressed as numbers of children (percentages in parentheses)*

	Vaccine lots used in randomised field trial		First two vaccine lots used after start of child vaccination programme in Sweden		Total
	Vaccine A (lot 3259 D)	Vaccine B (lot 6225)	Vaccine C (lot 002–1)	Vaccine D (lot 003–1)	
No of questionnaires returned	77	73	96	33	279
Fever 38·5–39·4°C	10 (13)	12 (16)	20 (21)	9 (27)	51 (18)
Fever ≥39·5°C	10 (13)	23 (32)	13 (14)	6 (18)	52 (19)
Rash	12 (16)	23 (32)	29 (30)	14 (42)	78 (28)

SEROLOGICAL RESULTS

Measles—Five out of 140 prevaccination samples tested by haemagglutination inhibition were found to be seropositive against measles. Postvaccination samples were obtained from 126 initially seronegative children; seroconversion was observed in 121 (96%). The figure shows the frequency distribution of postvaccination titres.

was also evaluated. Six of the 125 postvaccination sera tested by both methods were found to be positive in the neutralisation test, while four other sera were positive in the haemolysis in gel test only. The haemolysis in gel test is by far the simpler to carry out but may yield false positive results.[7] The serum neutralisation test is the more sensitive but is also laborious and not suitable for mass screening.[5,8]

Rubella—Two of the 142 prevaccination samples were seropositive. Seroconversion was seen in all but one of the 129 postvaccination sera tested (figure).

PRELIMINARY RESULTS IN VACCINATED SCHOOLCHILDREN

We record two early examples of experiences with the vaccination of 12 year old schoolchildren. In one school 1444 children were offered vaccination and 1366 accepted. The children were encouraged to report any postvaccination reaction. Fever was reported by 35 (2·6%), rash by 12 (0·9%), and arthralgia by 3 (0·2%). Mumps symptoms were seen in one, and neck lymphadenitis combined with fever and rash in two. In another school a group of 128 vaccinated children returned a form for daily recording of signs and symptoms occurring within 28 days after immunisation. Three of the children (2·3%) reported arthralgia, fever was notified by 9 (7·0%), and cervical lymphadenitis by one.

Comment

As in other countries, public opinion in Sweden is extremely sensitive to reports of major side effects of drugs and vaccines. Hence to secure a vaccine acceptance rate high enough to ensure the eventual elimination of measles, mumps, and rubella it was considered necessary to supply a valid estimate of the average incidence and clinical severity of the adverse reactions expected with the combined immunisation programme, especially among the youngest target group.

To enable us to compare the incidence of vaccine reactions reported during this trial with earlier experiences of the same vaccine in the United States we arranged our clinical findings according to an arbitrarily chosen time scheme closely similar to that used in a representative American study[9]—namely, by subdividing the total four week observation period into three unequal intervals of 0-4, 5-12, and 13-28 days after vaccine administration (table I).

In both studies most of the clinical symptoms (notified predominantly between days 5 and 12) were mild and lasted only a few days. Even during periods of high fever ($\geq 39{\cdot}5$°C)—found in about one fifth of the children—most of the children did not appear particularly sick or fretful and apparently behaved more or less normally.

The lack of a comparable control group precluded an exact evaluation of the true vaccine reaction rates, but the observed clustering of recorded clinical complaints five to 12 days after immunisation (table I) suggests that these were caused by the vaccine. The few fevers and rashes notified more than two weeks after vaccination probably reflect the expected patterns observed in children of that age.

The preliminary results in schoolchildren showed that fevers or other reactions were few and mild. The recorded incidences and severity of fever, rash, and arthralgia in the immunised 12 year old children were no higher than would normally be expected during any month in a school population of that age. Notwithstanding the difficulty of comparing the rates of side effects in the 18 month old children with those in the 12 year olds, the results do suggest that there may be an age difference in vaccine reactions. The apparently higher incidence of fever and other complaints at 18 months than at 12 years may to some extent have been due to the fact that most of the 12 year old children had experienced some of the diseases already; nevertheless, that cannot be the only explanation.

The difference in incidences of high fever and rash produced by the two vaccine batches used in this study was further investigated by continued recording of these symptoms at the same well baby clinics during several months after the start of the general immunisation programme, which used two further commercial batches of the combined vaccine (table II). The average incidence of high fever produced by vaccines C and D (pooled incidence 15%) was also significantly lower than that found for vaccine B ($p < 0{\cdot}01$). The overall incidence of high fever calculated for the total series of 279 children (52 cases; 19%) was considered to be the best available estimate of the incidence of high fever expected to occur as a side effect of vaccination in Swedish children aged 18 months.

Preliminary experience with the general child immunisation programme based on mandatory notifications to the Swedish Adverse Drug Reaction Committee of serious or unexpected side effects showed an almost negligible incidence of such reactions. The few that did occur bore no relation to the important complications of the three diseases that the mass vaccination campaign aims at preventing.

The satisfactory seroconversion rates (see figure) support the feasibility of complete eradication of the three diseases. The two step vaccination programme was chosen to avoid having a generation of young susceptible adults who have escaped natural exposure to the three viruses by virtue of the young vaccinees no longer being the usual source of infection. Such a development recently occurred in the United States. Outbreaks of measles[10] among university and college students occurred in 1982 and 1983, more than half of all the reported measles cases emanating from this group; over 20 000 students had to be vaccinated.

Of the few children who fail to seroconvert or escape immunisation at 18 months, most may—even after the elimination of natural infection—be expected to be vaccinated with a positive result at the second stage of the Swedish vaccination programme at the age of 12.

We thank Dr M R Hilleman, of Merck, Sharp, and Dohme Research Laboratories, USA, for providing combined vaccine A (lot 3259 D).

References

1 Taranger J. Vaccination programme for eradication of measles, mumps and rubella. *Lancet* 1982;ii:915-6.

2 Rabo E, Taranger J, Bengtsson E, Hallen B. Flygande start för vaccination mot mässling, påssjuka och röda hund. *Lakartidningen* 1982;**79**:2095-6.

3 Buynak EB, Weibel RE, Whitman JE, Stokes J, Hilleman MR. Combined live measles, mumps and rubella virus vaccine. *JAMA* 1969;**207**:2259-62.

4 Buynak EB, Hilleman MR. Live attenuated mumps virus vaccine. I. Vaccine development. *Proc Soc Exp Biol Med* 1966;**123**:768-75.

5 Kenny MT, Albright KL, Sanderson RP. Microneutralization test for the determination of mumps antibody in nerve cells. *Applied Microbiology* 1970;**20**:371-3.

6 Strannegård Ö, Grillner L, Lindberg J-M. Hemolysis-in-gel test, the demonstration of antibodies to rubella virus. *J Clin Microbiol* 1975;**1**:491-4.

7 Berger R, Just N. Comparison of five different tests for mumps antibodies. *Infection* 1980;**5**:180-3.

8 Christenson B, Heller L, Böttiger M. Immunizing effect and reactogenicity of two live, attenuated, mumps-virus vaccines. *J Biol Standard* (in press).

9 Stokes J, Weibel RE, Villarejos VM, Arguedas JA, Buynak EB, Hilleman MR. Trivalent combined measles-mumps-rubella vaccine. Findings in clinical laboratory studies. *JAMA* 1971;**218**:57-61.

10 Centers for Disease Control. Measles outbreaks on university campuses—Indiana, Ohio, Texas. *MMWR* 1983;**32**:15.

(*Accepted 10 May 1983*)

MEDICINES RESISTING POISON—Such medicines are called *Alexiteria*, and *Alexipharmaca*, which resist poison. Some of these resist poison by astral influence, and some physicians (though but few) can give a reason for it. These they have sorted into three ranks: 1. Such as strengthen nature, that so it may tame the poison the easier. 2. Such as oppose the poison by a contrary quality. 3. Such as violently thrust it out of doors. Such as strengthen nature against poison, either do it to the body universally, or else strengthen some particular part thereof. For many times one particular part of the body is most afflicted by the poison, suppose the stomach, liver, brain, or any other part: such as cherish and strengthen those parts, being weakened, may be said to resist poison. Such as strengthen the spirits, strengthen all the body. Sometimes poisons kill by their quality, and then are they to be corrected by their contraries. They which kill by cooling are to be remedied by heating, and the contrary; they which kill by corroding, are to be cured by lenitives, such as temper their acrimony. Those which kill by induration, or coagulation, require cutting medicines. Also because all poisons are in motion, neither stay they in one till they have seized and oppressed the fountain of life, therefore they have invented another faculty to stay their motion, viz terrene and emplastic. For they judge, if the poison light upon these medicines, they embrace them round with a viscous quality. Also they say the ways and passages are stopped by such means, to hinder their proceeding; take *Terra Lemnia* for one. Truly if these reasons be good, which I leave to future time to determine, it may be done for little cost. Some are of opinion that the safest way is to expel the poison out of the body, so soon as may be, and that is done by vomit, or purge, or sweat. You need not question the time, but do it as soon as may be; for there is no parlying with poison. Let vomiting be the first, purging the next, and sweating the last. This is general. But, If thou dost but observe the nature and motion of the venom, that will be thy best instructor. In the stomach it requires vomiting, in the blood and spirits, sweating, if the body be plethoric, bleeding, if full of evil humours, purging. Lastly, The cure being ended, strengthen the parts afflicted. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)